(b) instructions for determining that the subject is at increased risk of developing prostate cancer by

detecting the presence or absence of AS3 (Androgen Shutoff Gene 3) in said subject with at least one reagent; and

observing whether or not the subject is at increased risk of developing prostate cancer by observing if the presence of AS3 (Androgen Shutoff Gene 3) is or is not detected with said at least one reagent, wherein reduced or absent levels of AS3 (Androgen Shutoff Gene 3) indicates said subject is at increased risk of developing prostate cancer.

REMARKS

Claims 1-67 were pending in the application. Claims 1-2, 4-12, 47-49, and 51 have been examined and the remaining claims have been withdrawn from consideration. Applicants reserve the right to pursue these claims in one or more divisional applications.

Claims 5, 6, 47-49, and 51 have been amended. In particular, claims 5, 47, 49, and 51 have been amended to provide the full name of certain acronyms (*i.e.*, AS3), as suggested by the Examiner. Support for this amendment can be found, *e.g.*, at page 2, line 19 of the specification. Claim 5 has been amended to recite a specified percent identity. Support for this amendment can be found in the specification at, for example, page 4, lines 16-32. Claim 6 has been amended to specify the nature of stringent hybridization conditions as being "6x SSC at about 45°C followed by washing" and this language finds support at page 10, lines 3-8.

In addition, the specification has been amended to provide sequence identifiers, replace hyperlinks with a textual description or corresponding citation, and denote trademarks, as required by the Examiner. A substitute Sequence Listing is provided herewith. Support for the amendments is found in the specification and in the claims as originally filed. *No new matter has been added to the application.*

The foregoing amendments have been made solely to claim more fully the invention and/or to expedite prosecution of the present application and should in no way be construed as an acquiescence to any of the rejections in this or in any former Office Action issued in the present application. Applicants reserve the right to pursue the subject matter of the claims as originally filed in one or more subsequent applications.

Attached hereto as Appendix A, captioned "MARKED UP VERSION TO SHOW CHANGES MADE" is a marked-up version of the changes made to the specification and

the claims by the amendments presented herein. For the Examiner's convenience, a copy of the claims that will be pending upon entry of the present Amendment is also attached hereto as Appendix B.

Sequence Listing

The Examiner has indicated that the instant application fails to comply with the requirements of 37 C.F.R. §§1.821 through 1.825. Specifically, the Examiner states that, "the amino acid sequence disclosed on page 78 of the specification is of sufficient length to require [a sequence identifier]".

In accordance with 37 C.F.R. § 1.825, Applicants submit herewith substitute pages 1-24 that contain a substitute Sequence Listing for the above-referenced application. The specification has been amended to include reference to the specific sequence identifier (*i.e.*, SEQ ID NO: 6) which corresponds to the amino acid sequence recited in the specification.

In addition, Applicants submit concurrently herewith a computer-readable form (diskette) of the substitute Sequence Listing which, according to 37 C.F.R. §1.821(f), is identical in substance to the paper copy of the substitute Sequence Listing submitted herewith. *No new matter has been added.*

Objections to the Specification

The specification is objected to because, according to the Examiner, "[t]hroughhout the specification, the ATCC accession number(s) have been omitted."

Applicants submit that, pursuant to *In re Lundak*, Applicants have the right to make a deposit of a plasmid containing a nucleic sequence encoding the human AS3 sequence, prior to the issuance of the application (*In re Lundak* 723 F2d. 1216, 227 USPQ 90 (Fed. Cir. 1985)). Accordingly, Applicants reserve the right to amend the specification as originally filed to include the ATCC Deposit information for the claimed molecules prior to issuance of the application, if appropriate.

In addition, the Examiner states that all "embedded hyperlinks and/or other forms of browser-executable code" must be deleted pursuant to MPEP §608.01. Accordingly, Applicants have deleted such code where it appears in the specification, and where appropriate, replaced the code with a corresponding description or citation.

The Examiner also notes that all trademarks recited in the application should be demarcated. Accordingly, Applicants have amended the specification as suggested thereby obviating this objection.

Objections to the Claims

Claims 3 and 6-12 are objected to because, according to the Examiner, the "[claims are] incomplete because of the omission of the ATCC accession number".

As mentioned above, Applicants submit that pursuant to *In re Lundak*, Applicants have the right to make a deposit of a plasmid containing a nucleic sequence encoding the human AS3 sequence, prior to the issuance of the application (*In re Lundak, supra*). Accordingly, Applicants reserve the right to amend the claims as originally filed to include the ATCC Deposit information for the claimed molecules prior to issuance of the application, if appropriate.

Claim 51 is objected to because it is allegedly "drawn to the subject matter of a non-elected invention." Applicants note that the claim, as amended, is drawn to a kit comprising nucleic acids, *i.e.*, an elected invention, thereby obviating the objection.

Claim Rejections Under 35 U.S.C. §101

Claims 47 and 51 have been rejected under 35 U.S.C. §101 because, according to the Examiner, "the claimed invention is not supported by either a credible asserted utility or a well established utility." In particular, the Examiner alleges that the specification does not actually teach how the invention can be used to determine the likelihood that a mammal will develop a proliferative cell disorder by measuring the amount of mRNA encoding AS3 nor when and in which cells the invention (kit) should be used. With regard to claim 51, the Examiner states that the specification does not demonstrate a correlation between expression of AS3 and incidence of prostate cancer and that to make such a correlation would require a multi-centered epidemiological study.

Applicants respectfully disagree. Applicants assert that a specific, substantial, and well-established utility, which would have been credible to one skilled in the art at the time of the invention, is clearly disclosed in the instant specification.

The AS3 molecules of the present invention are involved in cancer, for example, cancers which are modulated by the presence of hormones (*e.g.*, prostate cancer, see, *e.g.*, pages 84-86). Applicants have described the structural and functional characteristics of the AS3 molecules in the instant specification in detail, at, for example, pages 76-79.

In addition, Applicants have shown that AS3 is expressed at high levels in prostate cells, but at low levels in prostate cells evidencing uncontrolled growth or proliferation, and more especially, prostate cancer cells unresponsive to therapy (see, *e.g.*, page 82-83). Accordingly, as set forth in the instant specification, the AS3 molecules of

the present invention act as targets/markers for diagnosing/prognosing a cell proliferative disorder in a subject. Accordingly, kits for carrying out the foregoing diagnosing/prognosing of a cell proliferative disorder, as currently claimed, have an immediate and credible use.

Moreover, the utilities asserted by Applicants are not "throw away" utilities (*e.g.*, use as a food supplement or cosmetic additive). To the contrary, the instant application teaches a specific biological role for the AS3 molecules of the invention, as well as the significance of this role in the treatment of proliferative disorders, for example cancer of the prostate (see, e.g., Examples 5 and 6). There is no evidence in the instant Office Action to establish that Applicants' assertions regarding the activities and/or utilities of the AS3 molecules as markers/modulators of cell proliferative disorders would not be considered credible to one of ordinary skill in the art. In addition, the Office Action is devoid of a reasoned explanation as to why the utilities asserted by Applicants would not be specific, substantial, and credible.

As the Examiner is aware, Applicants do not have to provide evidence sufficient to establish that an asserted utility is true "beyond reasonable doubt." *In re Irons*, 340 F.2d 974, 978, 144 USPQ 351, 354 (CCPA 1965). Instead, evidence will be sufficient, if considered as a whole, it leads a person of ordinary skill in the art to conclude that the asserted utility is more likely than not true. M.P.E.P. §2164.07.

Based on the ample teachings in Applicants' specification regarding the role and importance of AS3 molecules in cell proliferation related disorders, *e.g.*, prostate cancer (confirmed, for example, by working Example 6 where it is shown that the molecular ablation of AS3 using antisense allows human cancer cells to resume proliferating), Applicants respectfully submit that a person of ordinary skill in the art would conclude that Applicants' asserted utility is more likely than not true, which is all that is required under 35 U.S.C. §101. Conducting a multi-centered epidemiological study, as suggested by the Examiner, is simply not required for determining utility for the purposes of patentability.

In view of all of the foregoing, Applicants asserts that each of the utilities set forth in the specification for the invention as claimed are specific, credible and substantial and/or well-established utilities that would have been recognized as such by one of skill in the art at the time the application was filed. Therefore, the instant claims meet the requirements of 35 U.S.C. §101, and Applicants respectfully requests reconsideration and withdrawal of this rejection.

Claim Rejections Under 35 U.S.C. §112, First Paragraph

Rejection of Claims 47 and 51 Under 35 U.S.C. §112, First Paragraph

Claims 47 and 51 are also rejected under 35 U.S.C. §112, first paragraph, because, according to the Examiner, "since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention." In particular, the Examiner states that because other potential risk factors are associated with a proliferative cell disorder, the claimed invention cannot be predictive for any type of cancer, or any type of prostate cancer, especially in view of the fact that cancer is a complex and intractable disease. Accordingly, the Examiner concludes that the specification does not describe in such a way that one skilled in the art would know how to make and use the invention, absent undue experimentation.

Applicants respectfully disagree. Applicants assert that one of skill in the art would know how to make and use the claimed invention.

Claims 47 and 51 are directed to kits for, respectively, diagnosing the presence or prognosing the risk of disease, *e.g.*, a cell proliferative disease, by detecting the presence, absence, or altered levels of an AS3 molecule.

Applicants' specification discloses *ample* guidance as to how one of skill in the art would make and use the claimed invention. For example, Applicants discloses how the AS3 molecules of the invention can be used in both diagnostic and predictive applications (see, *e.g.*, the subsections entitled "Predictive Medicine"; "Diagnostic Assays"; "Prognostic Assays" (pages 59-67)). In addition, the specification also describes how to use the claimed invention to monitor the effects of a treatment regimen being given a patient having a disease, for example a cell proliferative disorder such as cancer, *e.g.*, prostate cancer, using the claimed invention.

The specification further teaches, in working Example 5, precisely how to use the AS3 molecule of the invention in the treatment of prostate cancer including, for example, as a marker of the efficacy of particular treatment. In addition, the specification teaches how the AS3 molecules of the claimed invention can also be used to select a particular treatment approach and if it is being successful, based on a determination of AS3 levels in a patient's tumor cells.

Still further, Applicants provide direct evidence in working Example 6 that the presence of AS3 in human cancer cells can slow cell proliferation, for example, in the presence of hormone, whereas the absence of AS3 (triggered using antisense) allows the

cancer cells to resume their uncontrolled growth. Accordingly, the correlation between AS3 molecules and cancer is made clear by Applicants' disclosure.

As the Examiner is aware, it is well known that enablement is not precluded by the necessity for some experimentation (see, *e.g.*, *In re Wands* 8 USPQ2d 1400-1407, 1404 (CAFC, 1988)). Applicants respectfully submit that any experimentation that may be required to use the claimed invention, *i.e.*, kits for the prognosing or diagnosing of a cancer, constitutes routine, not undue, experimentation, and therefore the specification clearly enables the pending claims.

Based on the foregoing teachings in Applicants' specification, the skilled artisan would have been able to practice the claimed invention using only routine experimentation. Accordingly, Applicants respectfully requests reconsideration and withdrawal of the rejection of claims 47 and 51 under 35 U.S.C. §112, first paragraph.

Rejection of Claims 1, 2, 4-12, 47-49 and 51 Under 35 U.S.C. §112, First Paragraph

Claims 1, 2, 4-12, 47-49 and 51 are also rejected under 35 U.S.C. §112, first paragraph because, according to the Examiner, the claimed "subject matter was not described in the specification in such a way as to enable one skilled in the art...to make and/or use the invention." In particular, the Examiner notes "discrepancies between the polynucleotide sequences disclosed in the specification and the corresponding sequences reported in the literature or submitted to publicly accessible databases." Specifically, the Examiner rejects claims 4-12 for lack of enablement. Still further, the Examiner alleges that Applicants were not fully in possession of the claimed invention.

Applicants respectfully disagree. Applicants assert that the claimed subject matter is sufficiently described such that one skilled in the art would know how to make and/or use the invention and that Applicants were fully in possession of the invention.

The alleged sequence discrepancies noted by the Examiner represent only minor sequencing differences between SEQ ID NO: 1 provided in the present application and GenBank Accession No. U95825 which was revised as evidenced by the revision history for this sequence (Appendix C). The correspondence between the sequences is greater that 99% as shown by the attached alignment (Appendix D). In addition, the sequence as represented by GenBank Accession No. U95825 would be more fully described and enabled upon submission of a corresponding ATCC deposit prior to issuance of the present application, if appropriate.

With regard to the sequencing differences between SEQ ID NO: 1 and Figure 1, SEQ ID NO; 1 simply provides a more comprehensive representation of the untranslated

3' end (*i.e.*, non-coding portion) of the molecule as compared to Figure 1. Applicants note throughout the specification that the scope of the present invention is intended to encompass variants of the AS3 molecules, for example, allelic variants, and that such variation can occur, for example, in the 3' untranslated region of the molecule. For example, Applicants disclose in Figure 6 (and SEQ ID NO: 4) an AS3 molecule having an additional 84 base pairs of sequence in the 3' untranslated region of the molecule. In addressing the remaining alleged discrepancy, Applicants provide in Appendix E, an alignment showing that the polypeptide sequence of SEQ ID NO: 2 and SEQ ID NO: 3 are, in fact, identical.

Under this same section, the Examiner also rejects claims 4-12 for lack of enablement. Claims 4-12 are directed to isolated AS3 nucleic acid molecules, vectors encoding the same, a host cell transfected with such a vector, and a method of producing an AS3 polypeptide by culturing the foregoing host cell under appropriate conditions. The Examiner alleges that, while the specification is enabling for an isolated nucleic acid as set forth in SEQ ID NO: 1, it does not enable an isolated nucleic acid that is at least 50% homologous to SEQ ID NO: 1 or a nucleic acid sequence encoding a polypeptide at least 45% homologous to the amino acid sequence of SEQ ID NO: 2, nor small fragments thereof.

Applicants respectfully disagree. However, in order to expedite prosecution, claims 4-12 have been amended to require that the claimed molecules (and thus, the vector comprising such a molecule (claims 9-10) as well as the host cell transfected with such an expression vector and method of using the host cell to produce an AS3 polypeptide which relies on the expression vector (claims 11-12)) to have at least "70% identity" with the sequence identifier recited in the claim.

Applicants' specification discloses *ample* guidance as to how one of skill in the art would make and use the claimed invention. For example, Applicants disclose how the nucleic acid molecules of the invention may be generated (pages 73-76 of the specification), how these nucleic acid molecules may be tested for activity (page 16, line 8, through page 17, line 2 of the specification), and how such nucleic acid molecules may be introduced into cells and used to produce an AS3 polypeptide, including AS3 polypeptides fused to a heterologous polypeptide (see, *e.g.*, the subsections entitled "Recombinant Expression Vectors", starting at page 38, line 1; "Host Cells" starting at page 42, line 9, and "Isolated AS3 Proteins" starting at page 26, line 14, as well as working Example 3).

The specification further teaches, for example, at pages 76-79, structural and

functional features characteristic of AS3 family members. For example, as indicated in the specification, AS3 family members can be identified by the presence of a DNA binding domain, a leucine zipper and kinase domain. Notably, Applicants demonstrate in working Example 3 entitled "Characterization of the AS3 Polypeptide Sequence" that the AS3 polypeptide can be expressed and purified and indeed comprises a functional kinase domain and DNA binding domain (see, *e.g.*, page 78, line 2 through page 79, line 26).

In addition, the claims as now amended, require that the claimed nucleic acid molecules have a significant degree of identity with the exemplified AS3 (Androgen Shutoff Gene 3) molecules. The specification provides sufficient guidance teaching the skilled artisan how AS3 nucleic acid and amino acid sequences can be selected and/or made. For example, the specification teaches the selection and/or making of homologues and orthologues, as well as variants (*e.g.*, allelic variants) and fragments of the AS3 molecules of the invention, at least, for example, at pages 18-20.

Furthermore, Applicants' disclosure provides methods by which a variant AS3 polypeptide or a fragment of an AS3 polypeptide can be assayed for AS3 biological activity, *e.g.*, kinase activity or DNA binding activity as noted above, but also the ability to suppress cancer cell proliferation, for example, as shown in working Examples 5 and 6 of the specification.

As the Examiner is aware, it is well known that enablement is not precluded by the necessity for some experimentation (see, *e.g.*, *In re Wands* 8 USPQ2d 1400-1407, 1404 (CAFC, 1988)). Applicants respectfully submits that any experimentation that may be required to select and/or make the claimed nucleic acid molecules, and subsequently practice methods of expressing and producing a polypeptide of the invention constitutes routine, not undue, experimentation, and therefore the specification clearly enables the pending claims.

Based on the foregoing teachings in Applicants' specification, the skilled artisan would have been able to practice the claimed invention using only routine experimentation. Accordingly, Applicants respectfully requests reconsideration and withdrawal of the rejection of claims 4-12 under 35 U.S.C. §112, first paragraph.

Rejection of Claims 2, 4-12, 47-49 and 51 Under 35 U.S.C. §112, First Paragraph

Claims 2, 4-12, 47-49 and 51 are also rejected under 35 U.S.C. §112, first paragraph as "containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention." In

particular, the Examiner is further of the opinion that the disclosure of SEQ ID NOS:1 and 3, encoding the polypeptide of SEQ ID NO:2 does not adequately describe the scope of the use of the claimed genus of polynucleotides. Further, the specification does not provide sufficient descriptive information, such as definitive structural (*e.g.*, intron/exon boundaries and their sequence) or functional features of the claimed genus of polypeptides.

Applicants respectfully disagree. Applicants submit that there is sufficient written description in Applicants' specification regarding AS3 polypeptide variants, *e.g.*, naturally occurring allelic variants, as well as AS3 polypeptides, to inform a skilled artisan that Applicants were in possession of the claimed invention at the time the application was filed. In order to meet the written description requirement of the first paragraph of 35 U.S.C. §112, it is not necessary that a patent specification describe each and every specific member of a genus recited in a claim.

The sufficiency of a disclosure in meeting the written description requirement of 35 U.S.C. §112 for claims to a genus of cDNAs was addressed in *The Regents of the University of California v. Eli Lilly and Co.*, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997), in which the Federal Circuit stated:

> [a] description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus ***or a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus*** [emphasis added].

Therefore, a claim to a genus of chemical compounds satisfies the written description requirement when its accompanying specification either defines by sequence a representative number of its members falling within the scope of the genus or when its accompanying specification defines the structural features common to a substantial portion of the genus. For reasons discussed in detail below, the instant specification satisfies this requirement for the claimed invention.

The instant specification describes in detail how an allelic variant may be identified or produced and teaches what kind of sequence variation functional and non-functional natural allelic variants of AS3 may have (see, for example, page 18, line 18, through page 21, line 2).

The Examiner is of the opinion that "[t]here is no description of the conserved regions which are critical to the structure and function of the genus claimed." Contrary to

the Examiner's assertions and as stated above, the instant specification teaches which regions of the AS3 molecules are likely essential for activity and which are not, and, thus, which regions of the AS3 molecules are amenable to alteration and which are not (see, *e.g.*, working Example 3). For example, as indicated in the specification, the kinase domains, leucine zipper, and DNA binding domains of an AS3 molecule are likely important for AS3 activity, and, thus, would not be varied greatly in a functional naturally occurring allelic variant.

Furthermore, the claims are not directed to any and/or all allelic variants of AS3 polypeptides but rather are directed only to those allelic variants that are encoded by a nucleic acid molecule which hybridizes to the complement of a nucleic acid molecule consisting of SEQ ID NO:1 or 3 under stringent conditions (*e.g.*, claim 6). The recited stringent hybridization conditions determine a specific subgenus of allelic variants in accordance with the invention, *i.e.*, the subgenus of allelic variants that are functional modulators of cell proliferation. As noted above, the instant specification fully describes the structural features of functional AS3 polypeptides, including, contrary to the Examiner's assertion, a full disclosure of the intron and exon boundaries and junction sequence of an AS3 molecule (see, *e.g.*, Fig. 6).

In summary, Applicants have described a genus of naturally occurring allelic variants based on structural features that are common to the genus. Moreover, the instant specification describes the amino acid sequences of an AS3 protein that possess these structural features. Thus, the instant specification satisfies the written description requirement for the claimed invention, based upon the standard articulated by the Federal Circuit in *The Regents of the University of California.*

Accordingly, Applicants respectfully requests reconsideration and withdrawal of the rejection of claims 2, 4-12, 47-49 and 51 under 35 U.S.C. § 112, first paragraph.

Claim Rejections Under 35 U.S.C. §112, Second Paragraph

Claims 4-12, 47-49, and 51 are rejected under 35 U.S.C. 112, second paragraph, because, according to the Examiner, the claims are "indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regards as the invention."

In particular, the Examiner states that the "metes and bounds" of claim 4 and 6-12 cannot be determined because claim 4 recites a nuclei acid allelic variant that encodes a polypeptide represented by SEQ ID NO:2. Applicants submit that one skilled in the art would recognize that the claims encompass allelic variants which, although differing at

the nucleic acid level, would still encode a polypeptide comprising the amino acid sequence set forth in SEQ ID NO: 2.

Claims 5 and 6-12 are also rejected because claim 5 (from which claims 6-12 depend) recites a nucleic acid molecule which encodes a fragment of a polypeptide comprising at least 15 contiguous amino acids of the amino acid sequence of SEQ ID NO: 2 and therefore it is unclear if the claim encompasses a protein which comprises 15 contiguous amino acids or a fragment which comprises at least 15 contiguous amino acids. Applicants submit that, while the claim encompasses both species, it would not be unclear to the skilled artisan as to the metes and bounds of the invention because of the guidance specifically recited in the claim, *i.e.*, that the sequence must be 15 contiguous amino acids of SEQ ID NO: 2.

Claim 6 is further rejected as vague and indefinite because the claim recites the phrase "under stringent conditions" which would encompass conditions of low to high permissiveness. Applicants respectfully disagree. However, without acquiescing to the rejection, Applicants have amended claim 6 to recite specific stringent hybridization conditions. Applicants note that the recited conditions are discussed in detail in the specification at page 20, lines 3-8.

Claims 47-49 and 51 are rejected as indefinite for reciting the laboratory designation of "AS3" as the sole means for identifying the molecules of the invention. Accordingly, Applicants have amended the claims to recite a parenthetical description of the term (which finds support in the specification at, *e.g.*, page 2, line 19) thereby obviating this aspect of the rejection.

Claim 47 is further rejected as vague and indefinite for using the phrase "a disease involving altered cell proliferation" and this is unclear because the degree of the altered cell proliferation is not provided. Applicants respectfully disagree. The specification provides several examples of cell lines, including working Example 6 using human cancer cells, which describe the degree of alteration in cell proliferation that can be observed. Furthermore, based on Applicants' disclosure in combination with the high degree of skill in the biotechnology arts, it would be readily apparent as to what type of altered cell proliferation is significant and the appropriate controls for so determining. For at least these reasons, the metes and bounds of the foregoing phrase would be clear to one of ordinary skill in the art.

Still further, claim 47 is rejected as vague and indefinite for use of the phrase "an increased likelihood" which is relative and absent any comparative standard. Again, for the reasons mentioned above, Applicants submit that the term is sufficiently definite in

that Applicants provide all the necessary teaching such that the skilled artisan would be apprised of the metes and bounds of the invention.

Claims 48 and 49 are rejected as indefinite because the claim does not relate back to the preamble. Accordingly Applicants have amended the claims, as suggested by the Examiner, thereby obviating this aspect of the rejection.

Claim 51 is rejected as vague and indefinite because the claim recites the phrase "at increased risk" and the term "reduced" which are relative terms which would not reasonably apprise the skilled artisan of the metes and bounds of the invention. Applicants respectfully disagree. As mentioned above, because of Applicants' disclosure in combination with the high degree of skill in the art, it would be readily apparent as to the necessary controls to determine if AS3 levels are sufficiently "reduced" such that the subject is determined to be "at increased risk."

Claim 51 is also rejected as vague and indefinite because it recites the phrase "probes that selectively bind to DNA encoding AS3" and is in improper format. Applicant have amended the claim to be in proper format and recite probes that "selectively bind to a *nucleic acid* encoding AS3." Applicants note that either the loss of an AS3 gene (DNA) or absent or reduced expression of AS3 (RNA) are disclosed by Applicants as being correlated with undesired cellular proliferation (see, *e.g.*, Examples 4 and 6). Accordingly, the amendment to the claims is fully supported by specification, and moreover, would be readily understood by the skilled artisan, as now amended.

At least for the foregoing reasons, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 4-12, 47-49, and 51 under 35 U.S.C. §112, second paragraph.

Claim Rejections Under 35 U.S.C. §102(a)

Rejection of Claims 5-12, 47-49, and 51 Under 35 U.S. C. §102(a)

Claims 5-12, 47-49, and 51 are rejected as anticipated by Geck *et al.* (*Journal of Steroid Biochemistry and Molecular Biology* 6:41-50 (1999)). Applicants respectfully disagree.

Applicants point out that Geck *et al.* (1999) represents Applicants' own work, published within the year before the filing of the present application, and thus cannot be used against Applicants under 35 U.S.C.§ 102(a). *In re Katz*, 687 F.2d 450, 215 USPQ 14 (CCPA 1958).

Accordingly, Applicants respectfully requests reconsideration and withdrawal of the rejection of claim 5-12, 47-49, and 51 under 35 U.S.C. §102(a), in view of Geck *et al.* (1999).

Rejection of Claims 4-9 and 47 Under 35 U.S.C. §102(a)

Claims 4-9 and 47 are rejected as anticipated by Genbank Accession No. AB023196 (Ohara *et al.*, Direct Submission, February 4, 1999). Applicants respectfully disagree.

Applicants point out that the sequence of Ohara *et al.* which, *e.g.*, allegedly comprises a nucleic acid sequence at least 250 nucleotides and aligns to Applicants' SEQ ID NO: 1, is not art as of the submission date of February 4, 1999 but rather is art only as of the publication date of the particular record, *i.e.*, April 20, 1999. Importantly, the publication of the Ohara *et al.* sequence at issue was well after Applicants' priority date of February 24, 1999. Applicants attach hereto as APPENDIX F a "Sequence Revision History" for the electronic record having Accession No. AB023196. The Examiner will note that prior to Applicants' priority date, the sequence of Ohara *et al.* was not available.

Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 4-9 and 47 under 35 U.S.C. §102(a) in view of Ohara *et al.*

Claim Rejections Under 35 U.S.C. §102(b)

Rejection of Claims 5-7, 9-11, 47, and 51 Under 35 U.S. C. §102(b)

Claims 5-7, 9-11, 47, and 51 are rejected as being anticipated by Geck *et al.* (*Journal of Steroid Biochemistry and Molecular Biology* 63:211-218 (1997)). The Examiner relies on Geck *et al.* (1997) as teaching the identification of an AS3 gene but notes that the actual sequence was not disclosed. The Examiner states, however, that the nucleic acid molecule is deemed the same as the nucleic acid molecule of the claims because the sequence is an inherent property of the nucleic acid molecule. Applicants respectfully disagree.

Applicants invention features isolated AS3 (Androgen Shutoff gene 3) nucleic acids (and polypeptides encoded thereby), the sequence of which is explicitly disclosed in the claims (*i.e.*, claims 5-7, 9-11). Remaining rejected claims 47 and 51 feature kits for, respectively, diagnosing or prognosing a subject for developing a cell proliferation disease, *e.g.*, prostate cancer, using an oligonucleotide probe that binds to an AS3 molecule of the invention.

By contrast, the Geck *et al.* (1997) reference fails to disclose any AS3 nucleic acid sequence (or polypeptide sequence) as presently claimed (*i.e.*, claims 5-7, 9-11) much less the use of such a nucleic acid sequence as a probe in a kit for diagnosing or prognosing a cell proliferative disease as presently claimed (claims 47 and 51).

As the Examiner is aware, for a prior art reference to anticipate a claimed invention in terms of 35 USC § 102, the prior art must teach *each and every element* of the claimed invention. *Lewmar Marine v. Barient*, 827 F.2d 744, 3 USPQ2d 1766 (Fed. Cir. 1987). Accordingly, as Geck *et al.* (1997) fail to teach each and every element of the instant claims, the reference is not anticipatory.

Applicants respectfully requests reconsideration and withdrawal of the rejection of claims 5-7, 9-11, 47, and 51 under 35 U.S.C. §102(b) in view of Geck *et al.* (1997).

Rejection of Claims 5-7, 47, and 51 Under 35 U.S. C. §102(b)

Claims 5-7, 47, and 51 are rejected as anticipated by Genbank Accession No. U95825 (Geck *et al.*, Direct Submission, March 28, 1997). Applicants respectfully disagree.

Applicants point out that the sequence of Geck *et al.* which, *e.g.*, allegedly comprises a nucleic acid sequence at least 50% homologous to Applicants' SEQ ID NO: 1, is not art as of the submission date of March 28, 1997 but rather is art only as of the publication date of the particular record, *i.e.*, March 30, 1999.

Importantly, the publication of the Geck *et al.* sequence at issue was well after Applicants' priority date of February 24, 1999. Applicants attach hereto as APPENDIX C a "Sequence Revision History" for the electronic record having Accession No. AB023196. The Examiner will note that prior to Applicants' priority date, the sequence of Geck *et al.* was not available.

Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 5-7, 47, and 51 under 35 U.S.C. §102(b) in view of Genbank Accession No. U95825.

Rejection of Claims 5-7, 9, 47, and 51 Under 35 U.S. C. §102(b)

Claims 5-7, 9, 47, and 51 are rejected as anticipated by Genbank Accession No. U50533 (Simard, Direct Submission, March 4, 1996). The Examiner relies on Simard as teaching a nucleic acid fragment of at least 250 nucleotides of a nucleic acid comprising Applicants' SEQ ID NO: 1 which encodes a polypeptide comprising an amino acid

sequence that is at least 45 % homologous to Applicants SEQ ID NO: 2. Applicants respectfully disagree.

As amended, claim 5 and corresponding dependent claims (*i.e.*, claims 6-7, and 9) feature AS3 molecules, specifically, isolated nucleic acids encoding an AS3 molecule, for example an AS3 polypeptide or portion thereof, and that such molecules must have at least 70% identity with the sequence identifiers recited in the claim. In addition, Applicants indicate in the specification that AS3 molecules of the instant claims (including claims 47 and 51) play a role in inhibition of cell proliferation, *e.g.*, in cells of the prostate (page 10, lines 21-30).

By contrast, Simard merely discloses a partial nucleic acid sequence without any indication as to what the nucleic acid encodes. Notably, Simard fails to disclose any polypeptide sequence or ascribe any function to the disclosed partial nucleic acid sequence. In addition, Simard fails to provide any teaching that the partial nucleic acid sequence disclosed could by used in a kit for diagnosing a cell proliferative disease (or risk for such a disease) as claimed by Applicants (claims 47 and 51).

As such, Simard fails to teach each and every element of the claimed invention and, accordingly, fails to anticipate the claimed invention. Applicants respectfully request reconsideration and withdrawal of the rejection of claims 5-7, 9, 47, and 51 under 35 U.S.C. § 102(b) in view of Simard.

Rejection of Claims 5-9 Under 35 U.S. C. §102(b)

Claims 5-9 are rejected as anticipated by Genbank Accession No. BF509252 (National Cancer Institute – Cancer Genome Anatomy Project, 1997). Applicants respectfully disagree.

Applicants respectfully point out that the sequence of Genbank Accession No. BF509252, which, *e.g.*, allegedly comprises a nucleic acid sequence at least 45% homologous to Applicants' SEQ ID NO: 2, is not art as of the submission date of 1997 but rather is art only as of the publication date of the particular record, *i.e.*, December 6, 2000.

Importantly, the publication of the sequence at issue was well after Applicants' priority date of February 24, 1999. Applicants attach hereto as APPENDIX G a "Sequence Revision History" for the electronic record having Accession No. BF509252. The Examiner will note that prior to Applicants' priority date, the sequence of Accession No. BF509252 was not available.

Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 5-9 under 35 U.S.C. §102(b) in view of Genbank Accession No. BF509252.

Claim Rejections Under 35 U.S.C. §103(a)

Rejection of Claims 1, 2, 5-12, 47-49, and 51 Under 35 U.S.C. §103(a)

Claims 1, 2, 5-12, 47-49, and 51 are rejected as being unpatentable over Geck *et al.* (1999). Applicants respectfully disagree.

As indicated above in Applicants' traversal of the Examiner's 35 U.S.C. §102(a) rejection in view of Geck *et al.* (1999), the reference at issue represents Applicants' own work published within the year before the filing of the present application, and thus is unavailable as a reference evidencing obviousness.

Accordingly, Applicants respectfully requests reconsideration and withdrawal of the rejection of claim 1, 2, 5-12, 47-49, and 51 under 35 U.S.C. §103(a) in view of Geck *et al.*

Rejection of Claims 5-12, 47-49, and 51 Under 35 U.S.C. §103(a)

Claims 5-12, 47-49, and 51 are rejected as being unpatentable over Geck *et al.* (1997). The Examiner acknowledges that Geck *et al.* (1997) do not disclose an actual sequence or a method for obtaining or isolating AS3 or a nucleotide sequence encoding AS3 fused to a heterologous polypeptide. However, the Examiner states that it would have been obvious to use the AS3 molecule of Geck *et al.* (1997) to "obtain a fusion protein comprising AS3 and the FLAG epitope by a process of culturing host cells transfected...to produce the fusion protein and isolate the fusion protein so produced." One would have been motivated make such a fusion to further elucidate the biologic function of AS3. Applicants respectfully disagree.

As noted above in Applicants' traversal of the Examiner's 35 U.S.C. §102 rejection, Applicants invention features isolated AS3 (Androgen shutoff gene 3) nucleic acids (and polypeptides encoded thereby), the sequence of which is explicitly disclosed in the claims (*e.g.*, claims 5-11). The remaining rejected claims are directed to methods for obtaining and isolating an AS3 polypeptide and kits for diagnosing or prognosing a disease related to the presence of an AS3 molecule (*e.g.*, claims 12, 47-49, and 51)

As the Examiner acknowledges, Geck *et al.* (1997) fail to disclose any AS3 nucleic acid sequence or polypeptide sequence or a method for obtaining, isolating, and making an AS3 polypeptide. Nonetheless, the Examiner states that it would have been

obvious how to make an AS3 polypeptide, for example, an AS3 fusion polypeptide for isolation. Applicants respectfully disagree.

Absent Applicants' actual sequencing of the entire AS3 gene and their deduction of the open reading frame of the gene encoding the AS3 polypeptide, one skilled in the art, using Geck *et al.* (1997), which provides no sequence information, would not have known which open reading frame to use in order to express the AS3 polypeptide much less genetically fuse it to a fusion protein for isolation. Indeed, the nucleic acid fragment mentioned (but not disclosed) in Geck is a short nucleotide fragment with no indication that the fragment even comprises an open reading frame, *i.e.*, encodes a polypeptide (or fragment thereof). Accordingly, there is no evidence that the AS3 molecule of Geck is capable of making a polypeptide, much less the polypeptide of the invention. Thus, based on Geck *et al.* (1997), it would not have been obvious to have arrived at the claimed invention.

As the Examiner is aware, a finding of obviousness relying on hindsight based on Applicants' disclosure is improper. Rather, the "critical step in analyzing the patentability of claims pursuant to section 103(a) is casting the mind back to the time of the invention, to consider the thinking of one of ordinary skill in the art, guided only by the prior art references and the then-accepted wisdom in the field." *In re Werner Kotzab*, 217 F.3d 1365, 1369, 55 USPQ2d 1313 (Fed. Cir. 2000).

Accordingly, Applicants respectfully requests reconsideration and withdrawal of the rejection of claim 5-12, 47-49, and 51 under 35 U.S.C. §103(a) in view of Geck *et al.* (1997).

Rejection of Claims 1, 2, 5-7, 47, and 51 Under 35 U.S.C. §103(a)

Claims 1, 2, 5-7, 47, and 49 are rejected as being unpatentable over GenBank Accession No. U95825 (Geck *et al.*, Direct Submission, March 28, 1997). Applicants respectfully disagree.

As indicated above in Applicants' traversal of the Examiner's 35 U.S.C. §102 rejection, Genbank Accession No. U95825 is not art as of the submission date of March 28, 1997 but rather is art only as of the publication date of the particular record, *i.e.*, March 30, 1999.

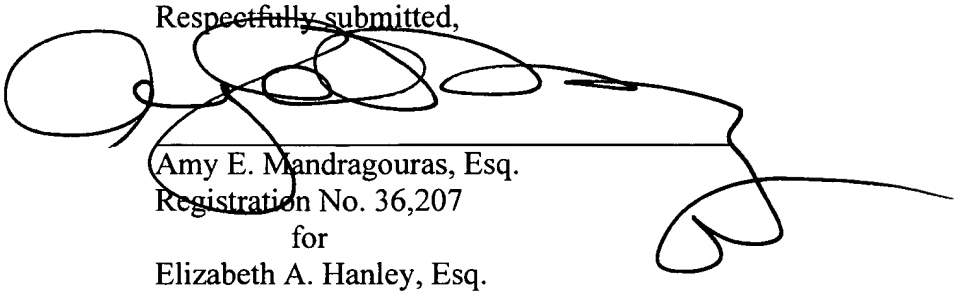
Importantly, the publication of the sequence at issue was well after Applicants' priority date of February 24, 1999. Accordingly, Genbank Accession No. U95825 is unavailable as a reference evidencing obviousness.

Accordingly, Applicants respectfully requests reconsideration and withdrawal of the rejection of claim 1, 2, 5-7, 47, and 51 under 35 U.S.C. §103(a).

CONCLUSION

In view of the foregoing, entry of the amendments and remarks herein, reconsideration and withdrawal of all rejections, and allowance of the instant application with all pending claims are respectfully solicited. If a telephone conversation with Applicants' attorney would help expedite the prosecution of the above-identified application, the Examiner is urged to call Applicants' attorney at (617) 227-7400.

Respectfully submitted,



Amy E. Mandragouras, Esq.
Registration No. 36,207
for
Elizabeth A. Hanley, Esq.
Registration No. 33,505
Attorney for Applicants

LAHIVE & COCKFIELD, LLP
28 State Street
Boston, MA 02109
Tel. (617) 227-7400

Dated: **May 28, 2002**